Treatment of Patients With Metastatic Colorectal Cancer in a Real-World Scenario: Probability of Receiving Second and Further Lines of Therapy and Description of Clinical Benefit

TREATMENT OF PATIENTS WITH METASTATIC COLORECTAL CANCER IN A REAL-WORLD SCENARIO: PROBABILITY OF RECEIVING SECOND AND FURTHER LINES OF THERAPY AND DESCRIPTION OF CLINICAL BENEFIT

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DISCLOSURE

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ABSTRACT

Background – The optimal therapeutic strategy for metastatic colorectal cancer (mCRC) patients is still a matter of debate. There are no prognostic variables indicating how many lines every single patient will receive, and whether later lines could be effective even when earlier were not.

Methods – We retrospectively collected data from 420 mCRC patients consecutively followed in our institution describing the proportion of patients who receive 2nd or later lines, and the chance for a line of treatment to be active when the previous line was not beneficial. For each line of treatment, we defined the "clinical benefit" as the probability of having not had evidence of disease progression 6 months after the start of chemotherapy.

Results – Of the 373 patients progressing after 1st line chemotherapy (1L), 277 received a second line (2L) (probability of being submitted to a 2L (P-2L)=74.3%): 143/226 received a 3L (P-3L=63.3%), and 56/122 were submitted to a 4L (P-4L=45.9%). Joint probabilities were: 2L 74.3%, 3L 47.0%, 4L 21.6%. 298/417 patients (71.5%) had a clinical benefit with 1L; 134/276 (48.6%) with 2L; 50/142 (35.2%) with 3L; and 12/48 (25.0%) with 4L. Taking all these data together, 31% of the patients who early progressed at 1L had the chance to have a clinical benefit with any of further lines.

Conclusion - Our study demonstrated that out of 4 patients submitted to a 1L, about 3 will receive a 2L, about 2 a 3L and nearly 1 a 4L. Later lines could be beneficial even though earlier therapies were not.

MICROASBSTRACT

There are no prognostic variables indicating how many lines every single patient will receive, and whether later lines could be effective. Among 420 subjects, joint probabilities for a patient submitted to 1L to receive further lines were: 2L 74.3%, 3L 47.0%, 4L 21.6%. Moreover, 31% of the patients who early progressed at 1L had a clinical benefit with later lines.

KEYWORDS

Colorectal cancer; advanced disease; third line therapy; fourth line therapy; clinical benefit; joint probabilities

INTRODUCTION

Colorectal cancer (CRC) is the second most frequently diagnosed cancer in women and the third in men, representing the 12.7% and 13.2% of all cancers worldwide, respectively, with an estimation of more than 690,000 deaths in 2012[1].

In the last two decades, the introduction of new and active agents lead to a progressive improvement in overall survival of metastatic CRC patients. Median life expectancy in patients treated with 5Fluorouracil (5FU) and folinic acid, the unique therapy option in early ‘90s, was 14 months[2]. The introduction of irinotecan and oxaliplatin in the last two decades lead to an improvement of overall survival that reached an average 21 months[3]. Finally, the description of clinical activity of targeted therapies such as bevacizumab, cetuximab, panitumumab and more recently aflibercept, regorafenib and ramucirumab raised the median life expectancy above 30 months (although some of these agents have been introduced in clinical practice very recently, and some others, like ramucirumab, are not yet available in many countries)[4-10]. The optimal therapeutic strategy is a matter of debate. Whether is better to administer front-line FOLFIRI or FOLFOX, or which targeted therapy (anti-vascular endothelial growth factor -VEGF- or anti-epidermal growth factor receptor -EGFR-) has to be administered in first line setting in the subgroup of patients who are in principle eligible for both, has not been established, yet. Moreover, the choice of the first-line therapy drives options in subsequent lines. As an example, if a patient receives FOLFIRI as front-line therapy, aflibercept could not be administered as second line treatment as it is permitted only in oxaliplatin-resistant patients. Some guidelines have recently been proposed[11], but the gray zones still remain. In fact, there are no prognostic indicators that may help clinicians in determining how many chemotherapy lines the single patient will be submitted to, and there is not a sufficient degree of certainty whether the same agent (especially biologicals) administered in later lines of therapy could be as effective as given earlier. On the other hand, it has been demonstrated that the maximal survival advantage is obtained in those patients who had had the chance to receive all the active

treatments[12], although these observations are affected by selection bias, considering that the exposition to higher number of drugs is clearly a time-dependent variable.

We collected data from metastatic CRC patients consecutively followed by the same institution from the time of first diagnosis of metastatic disease, in a “real life” setting. Aims of the study were the description of the proportion of patients submitted to second or further lines of chemotherapy, and the chance for a treatment to be active when the previous line was not beneficial.

PATIENTS AND METHODS

Study design

Clinical data and outcomes of all CRC patients treated at our Institution were retrieved from our institutional database, based on data prospectively collected since 1993. Data between January 1st , 2003 and December 31st , 2015 from patients who received first-line regimens were then extracted and entered into a new database specifically designed for the present study. The data extracted included patient demographics, performance status (PS) according to Eastern Cooperative Oncology Group (ECOG) scale, site of primitive (right: from cecum to splenic flexure; left: from splenic flexure to rectum); adjuvant treatment, time of first metastasis occurrence (metachronous vs synchronous), number of metastatic sites at the beginning of first-line treatment, date of chemotherapy start and disease progression for each line of therapy administered, and date of death or last follow-up visit.

The probability for a patient to receive each line of therapy was calculated dividing the total number of patients submitted to that line by the number of patients who progressed to the previous line. The relative probabilities were indicated as follows: P(2L) the probability to receive a second line, P(3L) the probability to receive a third line, and P(4L) the probability to receive a fourth line. Consequently, the joint probability for a patient submitted to a first-line to receive a third line was $P(2L \cap 3L) = P(2L)\ P(3L)$, and the joint probability for a patient to receive a fourth line was

$P(2L \cap 3L \cap 4L) = P(2L)\ P(3L)\ P(4L)$.

For each line of treatment, we defined the "clinical benefit" as the probability of having not had evidence of disease progression 6 months after the start of chemotherapy.

Statistical analyses

Differences between proportions were evaluated using the chi-square test with Yates correction, when appropriate. Statistical inferences of non-parametric unpaired parameters were performed with the Wilcoxon test when comparing two, or with the Kruskal-Wallis test when comparing three or more variables. Survival curves were plotted using the Kaplan-Meier method and compared using the log-rank test. Overall survival was calculated from the date of diagnosis of metastatic disease until death, or censored at the last follow-up visit. For each line of therapy, progression-free survival was calculated from the date of chemotherapy start to the date of progression or death. In case of no progression, patients were censored at the date of last follow-up visit.

All statistical computations were performed using GraphPad Prism version 6.0c for Mac OSX, SPSS for Windows Ver 22.0 and STATISTICA for Windows Ver. 8.0 softwares.

RESULTS

A total of 420 patients were included in the analyses. Their main characteristics are summarized in Table 1.

After the first line treatment, 277 patients out of the 373 who progressed received a second line (P(2L)=74.3%). After the second line, 143 out of 226 progressing patients received a third line (P(3L)=63.3%). After the third line, 56 out of 122 progressing patients received a fourth line (P(4L)=45.9%) (Table 2). As a whole, the joint probabilities for a patient who received a first line to receive further lines of therapy were: second line 74.3%, third line 47.0%, fourth line 21.6%.

The distribution of antineoplastic agents administered each line is summarized in Table 2.

Fluoropyrimidines were the backbone of the majority of treatments throughout the lines of therapy. As per internal protocol, oxaliplatin was administered mostly in first-line and irinotecan in second-line setting.

The proportion of patients submitted to each line of therapy did not differ according to the year of administration of the first-line (Table 3), nor to several tumor characteristics such as site of primitive, time of first metastasis occurrence, the number of metastatic sites and the administration of adjuvant treatment (Table 4). Only age was associated with a significantly different chance of receiving further lines: compared to patients older than 70 years, younger patients more frequently received a second line (77.7% *versus* 67.9%, p=0.04), a third line (72% *versus* 46.1; p=0.001), and a fourth line (49.5% *versus* 35.5%), even though this latter difference was not statistically significant (p=0.18) (Table 4).

Overall, the median number of lines received by patients was 2 (range 1-7). No difference was demonstrated when patients were stratified according to time of administration of first line (p=0.31), site of primitive (p=0.85), time of first metastasis occurrence (p=0.07), number of metastatic sites (p=0.12), and administration of adjuvant treatment (p=0.25). Younger patients received more later lines of therapy (median 2, range 1-7) than elderly patients (median 2, range 1-5: p=0.01).

At the time of data computation, 291 patients had died, with a median overall survival of 24.5 months. Survival outcomes according to patients' and tumors' characteristics are summarized in Table 5. Median progression free survival (PFS) for the first, second, third and fourth line were: 9.3, 5.7, 3.7, and 3.7 months, respectively.

As for clinical benefit, defined as PFS longer than 6 months, 298 out of 417 patients (71.5%) had a clinical benefit with first-line; 134/276 (48.6%) with second-line; 50/142 (35.2%) with third-line; and 12/48 (25.0%) with fourth line.

PFSs longer than 6 months were recorded also in patients without clinical benefit at the previous line (Table 6). In particular, nearly one third of the patients who progressed early at first-line had the

chance to have a clinical benefit to at least one further line.

DISCUSSION

Our analysis provides a description of the probability for patients with advanced CRC of receiving multiple lines of treatment in a real-life setting. We also show that the chance of obtaining a clinical benefit is not negligible, even in third or fourth line, and a clinical benefit can be obtained also in some of those patients who had experienced early failure of previous treatments.

Several panels of experts and scientific societies[13,14] have proposed clinical practice guidelines for patients with metastatic colorectal cancer, helping clinicians to choose the best treatment option according to the purpose they want to achieve and the line of therapy. Even though these guidelines suggest treatment options up to the third or even the fourth line of therapy, there are no predictive indicators that can discriminate, at the beginning of the sequence, which patients will actually receive further treatment after the failure of first-line. Indeed, the literature about the probability of a patient submitted to a first line to receive further lines of therapy is scanty, with only anecdotal papers describing the proportion of patients submitted to each line of therapy[15-17]. These studies, however, considered data from particular subsets of patients (elderly patients and patients living in rural zones). Moreover, they described the total number of patients submitted to a given line of therapy without weighting proportions according to the reason why the single patient did not receive a further line. In our study patients were prospectively followed and those without disease progression at the latest follow-up were not considered when computing the proportion of patients submitted to a particular line of therapy.

According to institutional protocols, oxaliplatin-based chemotherapy was the preferred first-line therapy, whereas irinotecan-based chemotherapy was a common choice for second-line treatments.

As it has already been demonstrated that the sequence of chemotherapy (FOLFOX as first line and FOLFIRI as second line or vice versa) does not influence overall outcomes[3], this characteristic does

not represent a bias of the study. Interestingly, in the same study exploring the “best” chemotherapy sequence, the proportion of patients submitted to a second line therapy in the two arms were 74.3% and 62.2%, respectively, in line with the results of our study.

No difference in the number of lines of therapy was evident when considering the year of first line administration and several prognostic factors such as site of primary, time of first metastasis appearance, previous adjuvant treatment, and number of metastatic sites. This could be explained by the relatively long natural history of the tumors demonstrated by the relatively long median overall survival of the entire population (>24 months), that permitted to administer later lines of therapy even to patients with unfavorable prognostic indicators. The unique difference we shown concerned elderly patients, who had lower chances to receive a second and a third line therapy, probably due to the concomitant presence of several comorbidities. The similar probabilities of an elderly patient to be submitted to a fourth line could be easily explained by the low number of subjects in each group and by an evident selection bias, as patients achieving a fourth line are those with a more indolent disease and favorable general conditions.

Of interest, approximately 25% of patients who did not beneficiate from a line of therapy (i.e. presented a disease progression shorter than 6 months) responded to one of the following chemotherapy lines (Table 6). In general, 31% of those patients with an early progression to a first-line beneficiated from at least one further chemotherapy line. This is in line with the observation reported by Grothey in 2004[12], where the maximal survival advantage was demonstrated in those patients who had the chance to receive all the active chemotherapy agents. Thus, the results of our study further support the opportunity of treating patients with good performance status even in case of a rapid progression from a previous line.

CONCLUSIONS

Our study shows that nearly three quarters of patients with advanced colorectal cancer submitted to a first-line therapy will receive a second line, approximately two out of four will receive a third line

and only 21% a fourth line. It will be of interest to identify some prognostic indicators able to discriminate those patients who will not receive later lines of therapies, along with predictive factors to select patients who may beneficiate from a more aggressive chemotherapy such as a triplet combined with a biological agent as front line therapy.

CLINICAL PRACTICE POINTS

- There are few studies reporting the probabilities for a patient with advanced colorectal cancer and submitted to a first line treatment to receive further lines.
- There is no data concerning the potential benefit of a later line even when earlier was not, especially in third and fourth line setting.
- We calculated the joint probabilities for a patients to be submitted to a subsequent line of therapy from a sample of 420 patients consecutively followed in one single institution in a “real-life” scenario. The probability for each line was calculated considering only those patients progressing after the previous line.
- Joint probabilities to be submitted to further lines were: second line 74.3%, third line 47.0%, fourth line 21.6%. As a whole, 31% of the patients who early progressed at 1L had the chance to have a clinical benefit with any of further lines.
- Half of the patients submitted to a first line is submitted to a third line, and this has to be taken into account when planning new trials in this patient setting.

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Table 1. Patients' characteristics

Year of fist-line start	**Number of patients**
2003-2006	140 (33.3%)
2007-2010	194 (46.2%)
2011-2015	86 (20.5%)
Age	
Median (range)	66 years (22-84)
<70 years	277 (66.0%)
>= 70 years	143 (34.0%)
Gender	
Male	249 (59.3%)
Female	171 (40.7%)
ECOG performance status	
0	135 (32.1%)
1	210 (50.0%)
2	56 (13.3%)
3	11 (2.6%)
Unknown	8 (2.0%)
Site of primitive	
Right	114 (27.9%)
Left	295 (72.1%)
Previous adjuvant treatment	
No	320 (76.2%)
Yes	100 (23.8%)

Time of first metastasis	
Metachronous	142 (33.8%)
Synchronous	278 (66.2%)
Number of metastatic sites	
1	240 (57.6%)
>1	177 (42.4%)

Table 2. Antitumoral agents according to line of therapy

Line of treatment	**Fluoro-pyrimidines**	**Oxaliplatin**	**Irinotecan**	**Anti-EGFR**	**Anti-VEGF**
1 (n=420)	419 (99.8%)	349 (83.1%)	45 (10.7%)	10 (2.4%)	20 (4.8%)
2 (n=277)	263 (94.9%)	63 (22.7%)	176 (63.5%)	30 (10.8%)	6 (2.2%)
3 (n=143)	113 (79.0%)	11 (7.7%)	61 (42.6%)	51 (35.7%)	10 (7.0%)
4 (n=56)	41 (73.2%)	4 (7.1%)	8 (14.3%)	7 (12.5%)	2 (3.6%)

Table 3. Proportion of patients submitted to each line of therapy stratified according to the time of

first-line administration

Line of treatment	**Total**	**Years 2003-2006 Number of patients / eligible***	**Years 2007-2010 Number of patients / eligible***	**Years 2011-2015 Number of patients / eligible***	**X^2 p****
1	420 (100%)	140 (100%)	194 (100%)	86 (100%)	-
2	277 / 373 (74.3)	96 / 126 (76.2%)	130 / 173 (75.1%)	51 / 74 (68.9%)	0.5
3	143 / 226 (63.3%)	45 / 75 (60.0%)	74 / 108 (68.5%)	24 / 43 (55.8%)	0.3
4	56 / 122 (45.9%)	17 / 39 (43.6%)	28 / 62 (45.2%)	11 / 21 (52.4%)	0.8

*Eligible patients are those progressing to the previous line of therapy

**X^2 p for differences according to year of first line start (contingency table 2x3)

Table 4. Proportion of patients submitted to each line of therapy stratified according to some patients' and tumors' characteristics. Data are expressed as Number of Patients (Number of patients / eligible* patients)

Line of treatment	**Age (years)**			**Site of primitive**			**Adjuvant**			**Time of first metastasis appearance**			**No of metastatic sites**		
	< 70	**>= 70**	**p****	**Right**	**Left**	**p****	**Yes**	**No**	**p****	**Synch**	**Met**	**p****	**1**	**>1**	**p****
1	277 (100%)	143 (100%)	-	114 (100%)	295 (100%)	-	100 (100%)	320 (100%)	-	278 (100%)	142 (100%)	-	240 (100%)	177 (100%)	-
2	188 / 242 (77.7%)	89 / 131 (67.9%)	0.04	75/102 (73.5%)	195/261 (74.7%)	0.8	60/88 (68.2%)	217/285 (76.1%)	0.1	191/247 (77.3%)	86/126 (68.3%)	0.06	160/210 (76.2%)	115/160 (71.9%)	0.3
3	108 / 150 (72.0%)	35 / 76 (46.1%)	0.001	38/59 (64.4%)	101/161 (62.7%)	0.8	31/53 (58.5%)	112/173 (64.7%)	0.4	102/152 (67.1%)	41/74 (55.4%)	0.09	93/135 (68.9%)	49/89 (55.1%)	0.04
4	45 / 91 (49.5%)	11 / 31 (35.5%)	0.18	14/33 (42.4%)	41/88 (46.6%)	0.8	13/28 (46.4%)	43/95 (45.3%)	0.9	39/87 (44.8%)	17/36 (47.2%)	0.8	36/79 (45.6%)	20/42 (47.6%)	0.8

*Eligible patients are those progressing to the previous line of therapy

** X^2 p

Table 5. Median survival for patients stratified according to patients' and tumors' characteristics.

	Median follow-up (months)	**Median OS (months)**
All patients	60.1	24.5
Date of first line treatment		
2003-2006	110	23.1
2007-2010	62.3	23.6
2011-2015	23.5	Not reached
Age		
<70 years	70.3	24.5
>= 70 years	42.1	24.7
Site of primitive		
Right	83.8	22.3
Left	60.1	25.9
Previous adjuvant treatment		
No	58.8	23.3
Yes	70.3	28.7
Time of first metastasis appearance		
Metachronous	60.1	29.6
Sinchronous	62.3	22.9
Number of metastatic sites		
1	70.3	29.3
>1	41.7	17.3

Table 6. Patients without progression at 6 months according to line of therapy and clinical benefit of previous line

	Patients with clinical benefit*
Second line	
Clinical benefit at first-line	118/215 (54.9%)
No Clinical benefit at first line	16/61 (26.2%)
Third line	
Clinical benefit at second-line	34/81 (42.0%)
No Clinical benefit at second line	16/61 (26.2%)
Fourth line	
Clinical benefit at third-line	8/25 (32.0%)
No Clinical benefit at third line	4/23 (17.4%)
Second or subsequent line of therapy	
Clinical benefit at first-line	132/215 (61.4%)
No Clinical benefit at first line	19/61 (31.1%)

*For each line, patients with a follow-up shorter than 6 months were excluded from the analysis